HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ACIPHEX safely and effectively. See full prescribing information for ACIPHEX.

ACIPHEX (rabeprazole sodium) tablet, delayed release for oral use
Initial U.S. Approval: 1999

RECENT MAJOR CHANGES

Indication and Usage (1.3) June/2008
Dosage and Administration, Pediatric Patients (2.7) June/2008
Use in Specific Populations, Pediatric Use (8.4) June/2008

INDICATIONS AND USAGE

ACIPHEX is a proton-pump inhibitor indicated for:
- Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD) (1.1)
- Maintenance of Healing of Erosive or Ulcerative GERD (1.2)
- Treatment of Symptomatic GERD (1.3)
- Healing of Duodenal Ulcers (1.4)
- *Helicobacter pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence (1.5)
- Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome (1.6)

ACIPHEX is a proton-pump inhibitor indicated for adolescent patients 12 years of age and above for:
- Short-term treatment of Symptomatic GERD (1.3)

DOSAGE AND ADMINISTRATION

ACIPHEX tablets should be swallowed whole. The tablets should not be chewed, crushed or split.

Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD) (2.1)
20 mg once daily

Maintenance of Healing of Erosive or Ulcerative GERD (2.2)
20 mg once daily

Treatment of Symptomatic GERD (2.3)
20 mg once daily

Healing of Duodenal Ulcers (2.4)
20 mg once daily after morning meal

***Helicobacter pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence** (2.5)
Three Drug Regimen *All three medications should be taken twice daily with morning and evening meals for 7 days*:
ACIPHEX 20 mg
Amoxicillin 1000 mg
Clarithromycin 500 mg

Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome (2.6)
Starting dose 60 mg once daily then adjust to patient needs

Short-term Treatment of GERD in Adolescent Patients 12 Years of Age and Above (2.7)
20 mg once daily for up to 8 weeks

DOSAGE FORMS AND STRENGTHS

- Tablets: 20 mg (3)

CONTRAINDICATIONS

- History of hypersensitivity to rabeprazole (4.1)

WARNINGS AND PRECAUTIONS

- Symptomatic response to therapy with rabeprazole does not preclude the presence of gastric malignancy. (5.4)
- Patients treated with a proton pump inhibitor and warfarin may need to be monitored for increases in INR and prothrombin time due to risk of abnormal bleeding. (5.5)

ADVERSE REACTIONS

- In the adult studies (4 to 8 weeks), there are no adverse reactions that occur at a rate greater than 5% and greater than placebo (6.1)
- In the adolescent patient studies, adverse reactions were similar to those found in adults (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai Inc. at 1-888-274-2378 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Increase INR and prothrombin times have been reported with concomitant use with warfarin. Patients need to be monitored (7.2)
- Rabeprazole has been shown to inhibit cyclosporine metabolism *in vitro* (7.3)
- ACIPHEX inhibits gastric acid secretion and may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, iron salts and digoxin) (7.4)
- ACIPHEX may reduce the plasma levels of atazanavir (7.4)

USE IN SPECIFIC POPULATIONS

- The safety and efficacy of ACIPHEX for GERD have not been established for pediatric patients less than 12 years of age.
- The safety and efficacy of ACIPHEX for the other adult indications have not been established for pediatric patients.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 02/2009

FULL PRESCRIBING INFORMATION: CONTENTS *

*** Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1 Healing of Erosive or Ulcerative GERD

ACIPHEX is indicated for short-term (4 to 8 weeks) treatment in the healing and symptomatic relief of erosive or ulcerative gastroesophageal reflux disease (GERD). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX may be considered.

1.2 Maintenance of Healing of Erosive of Ulcerative GERD

ACIPHEX is indicated for maintaining healing and reduction in relapse rates of heartburn symptoms in patients with erosive or ulcerative gastroesophageal reflux disease (GERD Maintenance). Controlled studies do not extend beyond 12 months.

1.3 Treatment of Symptomatic GERD

ACIPHEX is indicated for the treatment of daytime and nighttime heartburn and other symptoms associated with GERD in adults and adolescents 12 years of age and above.

1.4 Healing of Duodenal Ulcers

ACIPHEX is indicated for short-term (up to four weeks) treatment in the healing and symptomatic relief of duodenal ulcers. Most patients heal within four weeks.

1.5 *Helicobacter pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

ACIPHEX in combination with amoxicillin and clarithromycin as a three drug regimen, is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease (active or history within the past 5 years) to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. {See *CLINICAL STUDIES* (14.5) and *DOSAGE AND ADMINISTRATION* (2.5)}

In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted. {See *CLINICAL PHARMACOLOGY, Microbiology* (12.2) and the clarithromycin package insert, *CLINICAL PHARMACOLOGY, Microbiology*}

1.6 Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome
ACIPHEX is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

2. DOSAGE AND ADMINISTRATION
ACIPHEX tablets should be swallowed whole. The tablets should not be chewed, crushed, or split. ACIPHEX can be taken with or without food.

2.1 Healing of Erosive or Ulcerative GERD
The recommended adult oral dose is one ACIPHEX 20 mg delayed-release tablet to be taken once daily for four to eight weeks {See *INDICATIONS AND USAGE*.(1.1)}. For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of ACIPHEX may be considered.

2.2 Maintenance of Healing of Erosive or Ulcerative GERD
The recommended adult oral dose is one ACIPHEX 20 mg delayed-release tablet to be taken once daily. {See *INDICATIONS AND USAGE* (1.2)}.

2.3 Treatment of Symptomatic GERD
The recommended adult oral dose is one ACIPHEX 20 mg delayed-release tablet to be taken once daily for 4 weeks. {See *INDICATIONS AND USAGE* (1.3)} If symptoms do not resolve completely after 4 weeks, an additional course of treatment may be considered. The recommended adolescent dosing is listed in Section 2.7.

2.4 Healing of Duodenal Ulcers
The recommended adult oral dose is one ACIPHEX 20 mg delayed-release tablet to be taken once daily after the morning meal for a period up to four weeks. {See *INDICATIONS AND USAGE* (1.4)}. Most patients with duodenal ulcer heal within four weeks. A few patients may require additional therapy to achieve healing.

2.5 *Helicobacter pylori* Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

TABLE 1 THREE DRUG REGIMEN[a]:

Aciphex	20 mg	Twice Daily for 7 Days
Amoxicillin	1000 mg	Twice Daily for 7 Days
Clarithromycin	500 mg	Twice Daily for 7 Days

All three medications should be taken twice daily with the morning and evening meals.

[a] It is important that patients comply with the full 7-day regimen. {See CLINICAL STUDIES section.(14.5)}.

2.6 Treatment of Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome
The dosage of ACIPHEX in patients with pathologic hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once a day. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Some patients may require divided doses. Doses up to 100 mg QD and 60 mg BID have been administered. Some patients with Zollinger-Ellison syndrome have been treated continuously with ACIPHEX for up to one year.

2.7 Short-term Treatment of GERD in Adolescent Patients 12 Years of Age and Above
The recommended oral dose for adolescents 12 years of age and above is 20 mg once daily for up to 8 weeks {See *Pediatric Use* (8.4)}.

2.8 Elderly, Renal and Hepatic Impaired Patients
No dosage adjustment is necessary in elderly patients, in patients with renal disease or in patients with mild to moderate hepatic impairment. Administration of rabeprazole to patients with mild to moderate liver impairment resulted in increased exposure and decreased elimination. Due to the lack of clinical data on rabeprazole in patients with severe hepatic impairment, caution should be exercised in those patients.

3. DOSAGE FORMS AND STRENGTHS
20 mg light yellow enteric-coated delayed release tablets. The name and strength, in mg, (ACIPHEX 20) is imprinted on one side.

4. CONTRAINDICATIONS

4.1 Hypersensitivity to rabeprazole
Rabeprazole is contraindicated in patients with known hypersensitivity to rabeprazole, substituted benzimidazoles or to any component of the formulation.

4.2 Use of clarithromycin and hypersentivity to macrolide antibiotics
Clarithromycin is contraindicated in patients with known hypersensitivity to any macrolide antibiotic.

4.3 Concomitant use of clarithromycin with pimozide and cisapride
Concomitant administration of clarithromycin with pimozide and cisapride is contraindicated. There have been post-marketing reports of drug interactions when clarithromycin and/or erythromycin are co-administered with pimozide resulting in cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsade de pointes) most likely due to inhibition of hepatic metabolism of pimozide by erythromycin and clarithromycin. Fatalities have been reported. (Please refer to full prescribing information for clarithromycin.)

4.4 Amoxicillin and hypersensitivity to penicilllin
Amoxicillin is contraindicated in patients with a known hypersensitivity to any penicillin. (Please refer to full prescribing information for amoxicillin.)

5. WARNINGS AND PRECAUTIONS

5.1 Clarithromycin use in pregnant women
CLARITHROMYCIN SHOULD NOT BE USED IN PREGNANT WOMEN EXCEPT IN CLINICAL CIRCUMSTANCES WHERE NO ALTERNATIVE THERAPY IS APPROPRIATE. If pregnancy occurs while taking clarithromycin, the patient should be apprised of the potential hazard to the fetus. (See *WARNINGS* in prescribing information for clarithromycin.)

5.2 Anaphylactic Reactions associated with antibiotic use
Amoxicillin: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.
There have been well-documented reports of individuals with a history of penicillin hypersensitivity reactions that have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillin, cephalosporin, and other allergens. If an allergic reaction occurs, amoxicillin should be discontinued and the appropriate therapy instituted. (See *WARNINGS* in prescribing information for amoxicillin.)
SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

5.3 Pseudomembranous colitis associated with antibiotic use
Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin and amoxicillin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.
Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".
After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluid and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile colitis.*

5.4 Presence of Gastric malignancy
Symptomatic response to therapy with rabeprazole does not preclude the presence of gastric malignancy.
Patients with healed GERD were treated for up to 40 months with rabeprazole and monitored with serial gastric biopsies. Patients without *H. pylori* infection (221 of 326 patients) had no clinically important pathologic changes in the gastric mucosa. Patients with *H. pylori* infection at baseline (105 of 326 patients) had mild or moderate inflammation in the gastric body or mild inflammation in the gastric antrum. Patients with mild grades of infection or inflammation in the gastric body tended to change to moderate, whereas those graded moderate at baseline tended to remain stable. Patients with mild grades of infection or inflammation in the gastric antrum tended to remain stable. At baseline 8% of patients had atrophy of glands in the gastric body and 15% had atrophy in the gastric antrum. At endpoint, 15% of patients had atrophy of glands in the gastric body and 11% had atrophy in the gastric antrum. Approximately 4% of patients had intestinal metaplasia at some point during follow-up, but no consistent changes were seen.

5.5 Concomitant use with warfarin
Steady state interactions of rabeprazole and warfarin have not been adequately evaluated in patients. There have been reports of increased INR and prothrombin time in patients receiving a proton pump inhibitor and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with a proton pump inhibitor and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

6. ADVERSE REACTIONS
Worldwide, over 2900 patients have been treated with rabeprazole in Phase II-III clinical trials involving various dosages and durations of treatment.
Because clinical trials are conducted under varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1 Clinical Studies Experience
The data described below reflect exposure to ACIPHEX in 1064 patients exposed for up to 8 weeks. The studies were primarily placebo- and active-controlled trials in patients with Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD), Duodenal Ulcers and Gastric Ulcers. The population had a mean age of 53 years (range 18-89 years) and had a ratio of approximately 60% male/ 40% female. The racial distribution was 86% Caucasian, 8% African American, 2% Asian and 5% other. Most patients received either 10 mg, 20 mg or 40 mg/day of ACIPHEX.
An analysis of adverse reactions appearing in ≥ 2% of ACIPHEX patients (n= 1064) and with a greater frequency than placebo (n=89) in controlled North American and European acute treatment trials, revealed the following adverse reactions: pain (3% vs. 1%), pharyngitis (3% vs. 2%), flatulence (3% vs. 1%), infection (2% vs. 1%), and constipation (2% vs. 1%). The 3 long-term maintenance studies consisted of a total of 740 patients; at least 54% of patients were exposed to rabeprazole for 6 months while at least 33% were exposed for 12 months. Of the 740 patients, 247 (33%) and 241 (33%) patients received 10 mg and 20 mg of ACIPHEX, respectively, while 169 (23%) patients received placebo and 83 (11%) received omeprazole.
The safety profile of rabeprazole in the maintenance studies was consistent with what was observed in the acute studies
Other adverse events that were seen in controlled clinical trials which do not meet the above criteria (≥2% of ACIPHEX treated patients and > placebo) and for which there is a possibility of a causal relationship to rabeprazole include the following: headache, abdominal pain, diarrhea, dry mouth, dizziness, peripheral edema, hepatic enzyme increase, hepatitis, hepatic encephalopathy, myalgia, and arthralgia.
In a multicenter, open-label study of adolescent patients aged 12 to 16 years with a clinical diagnosis of symptomatic GERD or endoscopically proven GERD, the adverse event profile was similar to that of adults. The adverse reactions reported without regard to relationship to ACIPHEX that occurred in ≥ 2% of 111 patients were headache (9.9%), diarrhea (4.5%), nausea (4.5%), vomiting (3.6%), and abdominal pain (3.6%). The related reported adverse reactions that occurred in ≥ 2% of patients were headache (5.4%) and nausea (1.8%). There were no adverse reactions reported in these studies that were not previously observed in adults.
Combination Treatment with Amoxicillin and Clarithromycin: In clinical trials using combination therapy with rabeprazole plus amoxicillin and clarithromycin (RAC), no adverse reactions unique to this drug combination were observed. In the U.S. multicenter study, the most frequently reported drug related adverse reactions for patients who received RAC therapy for 7 or 10 days were diarrhea (8% and 7%) and taste perversion (6% and 10%), respectively.
No clinically significant laboratory abnormalities particular to the drug combinations were observed.
For more information on adverse reactions or laboratory changes with amoxicillin or clarithromycin, refer to their respective package prescribing information, *ADVERSE REACTIONS* section.

6.2 Postmarketing Experience
The following adverse reactions have been identified during postapproval use of ACIPHEX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: sudden death; coma and hyperammonemia; jaundice; rhabdomyolysis; disorientation and delirium; anaphylaxis; angioedema; bullous and other drug eruptions of the skin; severe dermatologic reactions, including toxic epidermal necrolysis (some fatal), Stevens-Johnson syndrome, and erythema multiforme; interstitial pneumonia; interstitial nephritis; and TSH elevations. In addition, agranulocytosis, hemolytic anemia, leukopenia, pancytopenia, and thrombocytopenia have been reported. Increases in prothrombin time/INR in patients treated with concomitant warfarin have been reported.

7. DRUG INTERACTIONS

7.1 Drugs metabolized by CYP450
Rabeprazole is metabolized by the cytochrome P450 (CYP450) drug metabolizing enzyme system. Studies in healthy subjects have shown that rabeprazole does not have clinically significant interactions with other drugs metabolized by the CYP450 system, such as warfarin and theophylline given as single oral doses, diazepam as a single intravenous dose, and phenytoin given as a single intravenous dose (with supplemental oral dosing). Steady state interactions of rabeprazole and other drugs metabolized by this enzyme system have not been studied in patients.

7.2 Warfarin
There have been reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including rabeprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death.{See *WARNINGS AND PRECAUTIONS* (5.5)}.

7.3 Cyclosporine
In vitro incubations employing human liver microsomes indicated that rabeprazole inhibited cyclosporine metabolism with an IC_{50} of 62 micromolar, a concentration that is over 50 times higher than the C_{max} in healthy volunteers following 14 days of dosing with 20 mg of rabeprazole. This degree of inhibition is similar to that by omeprazole at equivalent concentrations.

7.4 Compounds dependent on gastric pH for absorption
Rabeprazole produces sustained inhibition of gastric acid secretion. An interaction with compounds which are dependent on gastric pH for absorption may occur due to the magnitude of acid suppression observed with rabeprazole. For example, in normal subjects, co-administration of rabeprazole 20 mg QD resulted in an approximately 30% decrease in the bioavailability of ketoconazole and increases in the AUC and C_{max} for digoxin of 19% and 29%, respectively. Therefore, patients may need to be monitored when such drugs are taken concomitantly with rabeprazole. Co-administration of rabeprazole and antacids produced no clinically relevant changes in plasma rabeprazole concentrations.
Concomitant use of atazanavir and proton pump inhibitors is not recommended. Co-administration of atazanavir with proton pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and thereby reduce its therapeutic effect.

7.5 Drugs metabolized by CYP2C19
In a clinical study in Japan evaluating rabeprazole in patients categorized by CYP2C19 genotype (n=6 per genotype category), gastric acid suppression was higher in poor metabolizers as compared to extensive metabolizers. This could be due to higher rabeprazole plasma levels in poor metabolizers. Whether or not interactions of rabeprazole sodium with other drugs metabolized by CYP2C19 would be different between extensive metabolizers and poor metabolizers has not been studied.

7.6 Combined Administration with Clarithromycin
Combined administration consisting of rabeprazole, amoxicillin, and clarithromycin resulted in increases in plasma concentrations of rabeprazole and 14-hydroxyclarithromycin.{See *CLINICAL PHARMACOLOGY, Combined Administration with Antimicrobials* (12.3)}.
Concomitant administration of clarithromycin with pimozide and cisapride is contraindicated. (See *PRECAUTIONS* in prescribing information for clarithromycin.) (See *PRECAUTIONS* in prescribing information for amoxicillin.)

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Teratogenic Effects. Pregnancy Category B: Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 μg•hr/mL, about 13 times the human exposure at the recommended dose for GERD) and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 μg•hr/mL, about 8 times the human exposure at the recommended dose for GERD) and have revealed no evidence of impaired fertility or harm to the fetus due to rabeprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers
Following intravenous administration of ^{14}C-labeled rabeprazole to lactating rats, radioactivity in milk reached levels that were 2- to 7-fold higher than levels in the blood. It is not known if unmetabolized rabeprazole is excreted in human breast milk. Administration of rabeprazole to rats in late gestation and during lactation at doses of 400 mg/kg/day (about 195-times the human dose based on mg/m^2) resulted in decreases in body weight gain of the pups. Since many drugs are excreted in milk, and because of the potential for adverse reactions to nursing infants from rabeprazole, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use
Use of ACIPHEX in adolescent patients 12 years of age and above for short-term treatment of GERD is supported by a) extrapolation of results from adequate and well-controlled studies that supported the approval of ACIPHEX for adults {see *CLINICAL STUDIES* (14.1, 14.2, 14.3) and *INDICATIONS AND USAGE* (1.1, 1.2, 1.3)};b) safety and pharmacokinetic studies performed in adolescent patients {see *Pharmacokinetics, Pediatric* (12.3)}. The safety and effectiveness of ACIPHEX for the treatment of GERD patients <12 years of age have not been established. The safety and effectiveness of ACIPHEX for other pediatric indications have not been established.The safety and effectiveness of ACIPHEX for other uses have not been established in pediatric patients.
In a multicenter, randomized, open-label, parallel-group study, 111 adolescents patients 12 to 16 years of age with a clinical diagnosis of symptomatic GERD or suspected or endoscopically proven GERD were randomized and treated with either ACIPHEX 10 mg

or ACIPHEX 20 mg once daily for up to 8 weeks for the evaluation of safety and efficacy. The adverse event profile in adolescent patients was similar to that of adults. The related reported adverse events that occurred in ≥2 % of patients were headache (5.4%) and nausea (1.8%). There were no adverse reactions reported in these studies that were not previously observed in adults.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of ACIPHEX, 19% were 65 years and over, while 4% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Gender

Duodenal ulcer and erosive esophagitis healing rates in women are similar to those in men. Adverse reactions and laboratory test abnormalities in women occurred at rates similar to those in men.

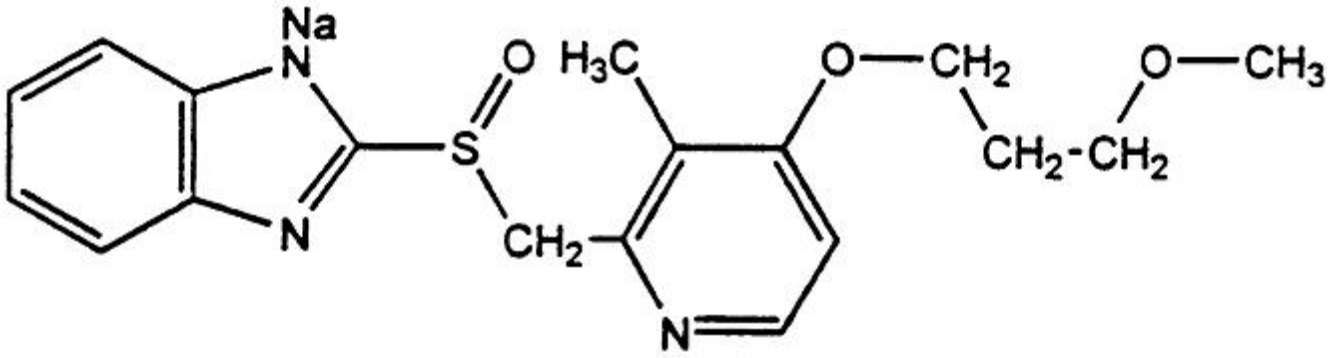
10. OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug. There has been no experience with large overdoses with rabeprazole. Seven reports of accidental overdosage with rabeprazole have been received. The maximum reported overdose was 80 mg. There were no clinical signs or symptoms associated with any reported overdose. Patients with Zollinger-Ellison syndrome have been treated with up to 120 mg rabeprazole QD. No specific antidote for rabeprazole is known. Rabeprazole is extensively protein bound and is not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

Single oral doses of rabeprazole at 786 mg/kg and 1024 mg/kg were lethal to mice and rats, respectively. The single oral dose of 2000 mg/kg was not lethal to dogs. The major symptoms of acute toxicity were hypoactivity, labored respiration, lateral or prone position and convulsion in mice and rats and watery diarrhea, tremor, convulsion and coma in dogs.

11. DESCRIPTION

The active ingredient in ACIPHEX Delayed-Release Tablets is rabeprazole sodium, a substituted benzimidazole that inhibits gastric acid secretion. Rabeprazole sodium is known chemically as 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1*H*-benzimidazole sodium salt. It has an empirical formula of $C_{18}H_{20}N_3NaO_3S$ and a molecular weight of 381.43. Rabeprazole sodium is a white to slightly yellowish-white solid. It is very soluble in water and methanol, freely soluble in ethanol, chloroform and ethyl acetate and insoluble in ether and n-hexane. The stability of rabeprazole sodium is a function of pH; it is rapidly degraded in acid media, and is more stable under alkaline conditions. The structural formula is:



ACIPHEX is available for oral administration as delayed-release, enteric-coated tablets containing 20 mg of rabeprazole sodium. Inactive ingredients of the 20 mg tablet are carnauba wax, crospovidone, diacetylated monoglycerides, ethylcellulose, hydroxypropyl cellulose, hypromellose phthalate, magnesium stearate, mannitol, propylene glycol, sodium hydroxide, sodium stearyl fumarate, talc, and titanium dioxide. Iron oxide yellow is the coloring agent for the tablet coating. Iron oxide red is the ink pigment.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazole proton-pump inhibitors) that do not exhibit anticholinergic or histamine H_2-receptor antagonist properties, but suppress gastric acid secretion by inhibiting the gastric H^+, K^+ATPase at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, rabeprazole has been characterized as a gastric proton-pump inhibitor. Rabeprazole blocks the final step of gastric acid secretion.

In gastric parietal cells, rabeprazole is protonated, accumulates, and is transformed to an active sulfenamide. When studied *in vitro*, rabeprazole is chemically activated at pH 1.2 with a half-life of 78 seconds. It inhibits acid transport in porcine gastric vesicles with a half-life of 90 seconds.

12.2 Pharmacodynamics

Antisecretory Activity

The anti-secretory effect begins within one hour after oral administration of 20 mg ACIPHEX. The median inhibitory effect of ACIPHEX on 24 hour gastric acidity is 88% of maximal after the first dose. ACIPHEX 20 mg inhibits basal and peptone meal-stimulated acid secretion versus placebo by 86% and 95%, respectively, and increases the percent of a 24-hour period that the gastric pH>3 from 10% to 65% (see table below). This relatively prolonged pharmacodynamic action compared to the short pharmacokinetic half-life (1-2 hours) reflects the sustained inactivation of the H^+, K^+ATPase.

TABLE 2 GASTRIC ACID PARAMETERS ACIPHEX VERSUS PLACEBO AFTER 7 DAYS OF ONCE DAILY DOSING

Parameter	**ACIPHEX (20 mg QD)**	**Placebo**
Basal Acid Output (mmol/hr)	0.4*	2.8
Stimulated Acid Output (mmol/hr)	0.6*	13.3
% Time Gastric pH>3	65*	10

*($p<0.01$ versus placebo)

Compared to placebo, ACIPHEX, 10 mg, 20 mg, and 40 mg, administered once daily for 7 days significantly decreased intragastric acidity with all doses for each of four meal-related intervals and the 24-hour time period overall. In this study, there were no statistically significant differences between doses; however, there was a significant dose-related decrease in intragastric acidity. The ability of rabeprazole to cause a dose-related decrease in mean intragastric acidity is illustrated below.

TABLE 3 AUC ACIDITY (MMOL•HR/L) ACIPHEX VERSUS PLACEBO ON DAY 7 OF ONCE DAILY DOSING (MEAN±SD)

	Treatment			
AUC interval (hrs)	**10 mg RBP (N=24)**	**20 mg RBP (N=24)**	**40 mg RBP (N=24)**	**Placebo (N=24)**
08:00 - 13:00	19.6±21.5*	12.9±23*	7.6±14.7*	91.1±39.7
13:00 - 19:00	5.6±9.7*	8.3±29.8*	1.3±5.2*	95.5±48.7
19:00 - 22:00	0.1±0.1*	0.1±0.06*	0.0±0.02*	11.9±12.5
22:00 - 08:00	129.2±84*	109.6±67.2*	76.9±58.4*	479.9±165
AUC 0-24 hours	155.5±90.6*	130.9±81*	85.8±64.3*	678.5±216

*($p<0.001$ versus placebo)

After administration of 20 mg ACIPHEX once daily for eight days, the mean percent of time that gastric pH>3 or gastric pH>4 after a single dose (Day 1) and multiple doses (Day 8) was significantly greater than placebo (see table below). The decrease in gastric acidity and the increase in gastric pH observed with 20 mg ACIPHEX administered once daily for eight days were compared to the same parameters for placebo, as illustrated below:

TABLE 4 GASTRIC ACID PARAMETERS ACIPHEX ONCE DAILY DOSING VERSUS PLACEBO ON DAY 1 AND DAY 8

	ACIPHEX 20 mg QD		**Placebo**	
Parameter	**Day 1**	**Day 8**	**Day 1**	**Day 8**
Mean AUC_{0-24} Acidity	340.8*	176.9*	925.5	862.4
Median trough pH (23-hr)[a]	3.77	3.51	1.27	1.38
% Time Gastric pH>3[b]	54.6*	68.7*	19.1	21.7
% Time Gastric pH>4[b]	44.1*	60.3*	7.6	11.0

[a] No inferential statistics conducted for this parameter.

* ($p<0.001$ versus placebo)

[b] Gastric pH was measured every hour over a 24-hour period.

Effects on Esophageal Acid Exposure

In patients with gastroesophageal reflux disease (GERD) and moderate to severe esophageal acid exposure, ACIPHEX 20 mg and 40 mg per day decreased 24-hour esophageal acid exposure. After seven days of treatment, the percentage of time that esophageal pH<4 decreased from baselines of 24.7% for 20 mg and 23.7% for 40 mg, to 5.1% and 2.0%, respectively. Normalization of 24-hour intraesophageal acid exposure was correlated to gastric pH>4 for at least 35% of the 24-hour period; this level was achieved in 90% of subjects receiving ACIPHEX 20 mg and in 100% of subjects receiving ACIPHEX 40 mg. With ACIPHEX 20 mg and 40 mg per day, significant effects on gastric and esophageal pH were noted after one day of treatment, and more pronounced after seven days of treatment.

Effects on Serum Gastrin

In patients given daily doses of ACIPHEX for up to eight weeks to treat ulcerative or erosive esophagitis and in patients treated for up to 52 weeks to prevent recurrence of disease the median fasting gastrin level increased in a dose-related manner. The group median values stayed within the normal range.

In a group of subjects treated daily with ACIPHEX 20 mg for 4 weeks a doubling of mean serum gastrin concentrations were observed. Approximately 35% of these treated subjects developed serum gastrin concentrations above the upper limit of normal.

In a study of CYP2C19 genotyped subjects in Japan, poor metabolizers developed statistically significantly higher serum gastrin concentrations than extensive metabolizers.

Effects on Enterochromaffin-like (ECL) Cells

Increased serum gastrin secondary to antisecretory agents stimulates proliferation of gastric ECL cells which, over time, may result in ECL cell hyperplasia in rats and mice and gastric carcinoids in rats, especially in females (see *Carcinogenesis, Mutagenesis, Impairment of Fertility* (13.1)}.

In over 400 patients treated with ACIPHEX (10 or 20 mg/day) for up to one year, the incidence of ECL cell hyperplasia increased with time and dose, which is consistent with the pharmacological action of the proton-pump inhibitor. No patient developed the adenomatoid, dysplastic or neoplastic changes of ECL cells in the gastric mucosa. No patient developed the carcinoid tumors observed in rats.

Endocrine Effects

Studies in humans for up to one year have not revealed clinically significant effects on the endocrine system. In healthy male volunteers treated with ACIPHEX for 13 days, no clinically relevant changes have been detected in the following endocrine parameters examined: 17 β-estradiol, thyroid stimulating hormone, tri-iodothyronine, thyroxine, thyroxine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteotrophic hormone, prolactin, somatotrophic hormone, dehydroepiandrosterone, cortisol-binding globulin, and urinary 6β-hydroxycortisol, serum testosterone and circadian cortisol profile.

Other Effects

In humans treated with ACIPHEX for up to one year, no systemic effects have been observed on the central nervous, lymphoid, hematopoietic, renal, hepatic, cardiovascular, or respiratory systems. No data are available on long-term treatment with ACIPHEX and ocular effects.

Microbiology

The following *in vitro* data are available but the clinical significance is unknown.

Rabeprazole sodium, amoxicillin and clarithromycin as a three drug regimen has been shown to be active against most strains of *Helicobacter pylori* in vitro and in clinical infections as described in the *CLINICAL STUDIES* (14) and *INDICATIONS AND USAGE* (1)sections.

Helicobacter pylori

Susceptibility testing of *H. pylori* isolates was performed for amoxicillin and clarithromycin using agar dilution methodology[1], and minimum inhibitory concentrations (MICs) were determined. The clarithromycin and amoxicillin MIC values should be interpreted according to the following criteria:

TABLE 5 INTERPRETATION OF CLARITHROMYCIN AND AMOXICILLIN MIC VALUES

Clarithromycin MIC (μg/mL) [a]	**Interpretation**
≤0.25 0.5 ≥1.0	Susceptible (S) Intermediate (I) Resistant (R)
Amoxicillin MIC (μg/mL) [a,b]	Interpretation
≤0.25	Susceptible (S)

[a] These are breakpoints for the agar dilution methodology and they should not be used to interpret results using alternative methods.

[b] There were not enough organisms with MICs > 0.25 μg/mL to determine a resistance breakpoint.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard clarithromycin and amoxicillin powders should provide the following MIC values:

TABLE 6 MIC VALUES FOR STANDARD CLARITHROMYCIN AND AMOXICILLIN POWDERS

Microorganism	Antimicrobial Agent	MIC (μg/mL)[a]
H. pylori ATCC 43504	Clarithromycin	0.015 - 0.12 μg/mL
H. pylori ATCC 43504	Amoxicillin	0.015 - 0.12 μg/mL

[a] These are quality control ranges for the agar dilution methodology and they should not be used to control test results obtained using alternative methods.

Incidence of Antibiotic-Resistant Organisms Among Clinical Isolates

***Pretreatment Resistance*:** Clarithromycin pretreatment resistance rate (MIC ≥ 1 μg/mL) to *H. pylori* was 9% (51/ 560) at baseline in all treatment groups combined. A total of > 99% (558/560) of patients had *H. pylori* isolates which were considered to be susceptible (MIC ≤ 0.25 μg/mL) to amoxicillin at baseline. Two patients had baseline *H. pylori* isolates with an amoxicillin MIC of 0.5 μg/mL.
Clarithromycin Susceptibility Test Results and Clinical/Bacteriologic Outcomes: For the U.S. multicenter study, the baseline H. pylori clarithromycin susceptibility results and the H. pylori eradication results post-treatment are shown in the table below:
TABLE 7 CLARITHROMYCIN SUSCEPTIBILITY TEST RESULTS AND CLINICAL/BACTERIOLOGIC OUTCOMES A FOR A THREE DRUG REGIMEN (RABEPRAZOLE 20 MG TWICE DAILY, AMOXICILLIN 1000 MG TWICE DAILY, AND CLARITHROMYCIN 500 MG TWICE DAILY FOR 7 OR 10 DAYS)

Days of RAC Therapy	Clarithromycin Pretreatment Results	Total Number	*H. pylori* Negative (Eradicated)	*H. pylori* Positive (Persistent) Post-Treatment Susceptibility Results			
				S[b]	I[b]	R[b]	No MIC
7	Susceptible [b]	129	103	2	0	1	23
7	Intermediate [b]	0	0	0	0	0	0
7	Resistant [b]	16	5	2	1	4	4
10	Susceptible [b]	133	111	3	1	2	16
10	Intermediate [b]	0	0	0	0	0	0
10	Resistant [b]	9	1	0	0	5	3

[a] Includes only patients with pretreatment and post-treatment clarithromycin susceptibility test results.

[b] Susceptible (S) MIC ≤ 0.25 μg/mL, Intermediate (I) MIC = 0.5 μg/mL, Resistant (R) MIC ≥ 1 μg/mL

Patients with persistent *H. pylori* infection following rabeprazole, amoxicillin, and clarithromycin therapy will likely have clarithromycin resistant clinical isolates. Therefore, clarithromycin susceptibility testing should be done when possible. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted.
Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes: In the U.S. multicenter study, a total of >99% (558/560) of patients had *H. pylori* isolates which were considered to be susceptible (MIC ≤ 0.25 μg/mL) to amoxicillin at baseline. The other 2 patients had baseline *H. pylori* isolates with an amoxicillin MIC of 0.5 μg/mL, and both isolates were clarithromycin-resistant at baseline; in one case the *H. pylori* was eradicated. In the 7- and 10-day treatment groups 75% (107/145) and 79% (112/142), respectively, of the patients who had pretreatment amoxicillin susceptible MICs (≤0.25 μg/mL) were eradicated of *H. pylori*. No patients developed amoxicillin-resistant *H. pylori* during therapy.

12.3 Pharmacokinetics

ACIPHEX delayed-release tablets are enteric-coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach relatively intact. After oral administration of 20 mg ACIPHEX, peak plasma concentrations (C_{max}) of rabeprazole occur over a range of 2.0 to 5.0 hours (T_{max}). The rabeprazole C_{max} and AUC are linear over an oral dose range of 10 mg to 40 mg. There is no appreciable accumulation when doses of 10 mg to 40 mg are administered every 24 hours; the pharmacokinetics of rabeprazole are not altered by multiple dosing. The plasma half-life ranges from 1 to 2 hours.
Absorption: Absolute bioavailability for a 20 mg oral tablet of rabeprazole (compared to intravenous administration) is approximately 52%. When rabeprazole is administered with a high fat meal, its T_{max} is variable and may delay its absorption up to 4 hours or longer, however, the C_{max} and the extent of rabeprazole absorption (AUC) are not significantly altered. Thus rabeprazole may be taken without regard to timing of meals.
Distribution: Rabeprazole is 96.3% bound to human plasma proteins.

Metabolism: Rabeprazole is extensively metabolized. A significant portion of rabeprazole is metabolized via systemic nonenzymatic reduction to a thioether compound. Rabeprazole is also metabolized to sulphone and desmethyl compounds via cytochrome P450 in the liver. The thioether and sulphone are the primary metabolites measured in human plasma. These metabolites were not observed to have significant antisecretory activity. *In vitro* studies have demonstrated that rabeprazole is metabolized in the liver primarily by cytochromes P450 3A (CYP3A) to a sulphone metabolite and cytochrome P450 2C19 (CYP2C19) to desmethyl rabeprazole. CYP2C19 exhibits a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3 to 5% of Caucasians and 17 to 20% of Asians). Rabeprazole metabolism is slow in these sub-populations, therefore, they are referred to as poor metabolizers of the drug.

Elimination: Following a single 20 mg oral dose of ^{14}C-labeled rabeprazole, approximately 90% of the drug was eliminated in the urine, primarily as thioether carboxylic acid; its glucuronide, and mercapturic acid metabolites. The remainder of the dose was recovered in the feces. Total recovery of radioactivity was 99.8%. No unchanged rabeprazole was recovered in the urine or feces.

Geriatric: In 20 healthy elderly subjects administered 20 mg rabeprazole once daily for seven days, AUC values approximately doubled and the C_{max} increased by 60% compared to values in a parallel younger control group. There was no evidence of drug accumulation after once daily administration. {see *USE IN SPECIAL POPULATIONS Geriatric Use* (8.5)}.

Pediatric: The pharmacokinetics of rabeprazole was studied in 12 adolescent patients with GERD 12 to 16 years of age, in a multicenter study. Patients received rabeprazole 20 mg once daily for five or seven days. An approximate 40% increase in exposure was noted following 5 to 7 days of dosing compared with the exposure after 1 day dosing. Pharmacokinetic parameters in adolescent patients with GERD 12 to 16 years of age were within the range observed in healthy adult volunteers.

Gender and Race: In analyses adjusted for body mass and height, rabeprazole pharmacokinetics showed no clinically significant differences between male and female subjects. In studies that used different formulations of rabeprazole, $AUC_{0-\infty}$ values for healthy Japanese men were approximately 50-60% greater than values derived from pooled data from healthy men in the United States.

Renal Disease: In 10 patients with stable end-stage renal disease requiring maintenance hemodialysis (creatinine clearance ≤5 mL/min/1.73 m^2), no clinically significant differences were observed in the pharmacokinetics of rabeprazole after a single 20 mg oral dose when compared to 10 healthy volunteers. (see *DOSAGE AND ADMINISTRATION* (2.7)}

Hepatic Disease: In a single dose study of 10 patients with chronic mild to moderate compensated cirrhosis of the liver who were administered a 20 mg dose of rabeprazole, AUC_{0-24} was approximately doubled, the elimination half-life was 2- to 3-fold higher, and total body clearance was decreased to less than half compared to values in healthy men.

In a multiple dose study of 12 patients with mild to moderate hepatic impairment administered 20 mg rabeprazole once daily for eight days, $AUC_{0-\infty}$ and C_{max} values increased approximately 20% compared to values in healthy age- and gender-matched subjects. These increases were not statistically significant.

No information exists on rabeprazole disposition in patients with severe hepatic impairment. Please refer to the *DOSAGE AND ADMINISTRATION* section (2.7) for information on dosage adjustment in patients with hepatic impairment.

Combined Administration with Antimicrobials: Sixteen healthy volunteers genotyped as extensive metabolizers with respect to CYP2C19 were given 20 mg rabeprazole sodium, 1000 mg amoxicillin, 500 mg clarithromycin, or all 3 drugs in a four-way crossover study. Each of the four regimens was administered twice daily for 6 days. The AUC and Cmax for clarithromycin and amoxicillin were not different following combined administration compared to values following single administration. However, the rabeprazole AUC and Cmax increased by 11% and 34%, respectively, following combined administration. The AUC and Cmax for 14-hydroxyclarithromycin (active metabolite of clarithromycin) also increased by 42% and 46%, respectively. This increase in exposure to rabeprazole and 14-hydroxyclarithromycin is not expected to produce safety concerns.

13. NONCLINICAL PHARMACOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 88/104-week carcinogenicity study in CD-1 mice, rabeprazole at oral doses up to 100 mg/kg/day did not produce any increased tumor occurrence. The highest tested dose produced a systemic exposure to rabeprazole (AUC) of 1.40 μg•hr/mL which is 1.6 times the human exposure (plasma $AUC_{0-\infty}$ = 0.88 μg•hr/mL) at the recommended dose for GERD (20 mg/day). In a 28-week carcinogenicity study, rabeprazole at oral doses up to 200 mg/kg was orally given to male and female p53+/- transgenic mice (approximately 17-24x human exposure at MRD based on AUC) did not cause an increase in the incidence rates of tumors, while gastric mucosal thickening and hyperplasia, secondary to the pharmacological action, were observed. In a 104-week carcinogenicity study in Sprague-Dawley rats, males were treated with oral doses of 5, 15, 30 and 60 mg/kg/day and females with 5, 15, 30, 60 and 120 mg/kg/day. Rabeprazole produced gastric enterochromaffin-like (ECL) cell hyperplasia in male and female rats and ECL cell carcinoid tumors in female rats at all doses including the lowest tested dose. The lowest dose (5 mg/kg/day) produced a systemic exposure to rabeprazole (AUC) of about 0.1 μg•hr/mL which is about 0.1 times the human exposure at the recommended dose for GERD. In male rats, no treatment related tumors were observed at doses up to 60 mg/kg/day producing a rabeprazole plasma exposure (AUC) of about 0.2 μg•hr/mL (0.2 times the human exposure at the recommended dose for GERD).

Rabeprazole was positive in the Ames test, the Chinese hamster ovary cell (CHO/HGPRT) forward gene mutation test and the mouse lymphoma cell (L5178Y/TK+/-) forward gene mutation test. Its demethylated-metabolite was also positive in the Ames test.

Rabeprazole was negative in the *in vitro* Chinese hamster lung cell chromosome aberration test, the *in vivo* mouse micronucleus test, and the *in vivo* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) tests.

Rabeprazole at intravenous doses up to 30 mg/kg/day (plasma AUC of 8.8 μg•hr/mL, about 10 times the human exposure at the recommended dose for GERD) was found to have no effect on fertility and reproductive performance of male and female rats.

14. CLINICAL STUDIES

14.1 Healing of Erosive or Ulcerative GERD

In a U.S., multicenter, randomized, double-blind, placebo-controlled study, 103 patients were treated for up to eight weeks with placebo, 10 mg, 20 mg or 40 mg ACIPHEX QD. For this and all studies of GERD healing, only patients with GERD symptoms and at least grade 2 esophagitis (modified Hetzel-Dent grading scale) were eligible for entry. Endoscopic healing was defined as grade 0 or 1. Each rabeprazole dose was significantly superior to placebo in producing endoscopic healing after four and eight weeks of treatment. The percentage of patients demonstrating endoscopic healing was as follows:

TABLE 8 HEALING OF EROSIVE OR ULCERATIVE GASTROESOPHAGEAL REFLUX DISEASE (GERD) PERCENTAGE OF PATIENTS HEALED

Week	10 mg ACIPHEX QD N=27	20 mg ACIPHEX QD N=25	40 mg ACIPHEX QD N=26	Placebo N=25
4	63%*	56%*	54%*	0%
8	93%*	84%*	85%*	12%

*($p<0.001$ versus placebo)

In addition, there was a statistically significant difference in favor of the ACIPHEX 10 mg, 20 mg, and 40 mg doses compared to placebo at Weeks 4 and 8 regarding complete resolution of GERD heartburn frequency ($p\leq0.026$). All ACIPHEX groups reported significantly greater rates of complete resolution of GERD daytime heartburn severity compared to placebo at Weeks 4 and 8 ($p\leq0.036$). Mean reductions from baseline in daily antacid dose were statistically significant for all ACIPHEX groups when compared to placebo at both Weeks 4 and 8 ($p\leq0.007$).

In a North American multicenter, randomized, double-blind, active-controlled study of 336 patients, ACIPHEX was statistically superior to ranitidine with respect to the percentage of patients healed at endoscopy after four and eight weeks of treatment (see table below):

TABLE 9 HEALING OF EROSIVE OR ULCERATIVE GASTROESOPHAGEAL REFLUX DISEASE (GERD) PERCENTAGE OF PATIENTS HEALED

Week	ACIPHEX 20 mg QD N=167	Ranitidine 150 mg QID N=169
4	59%*	36%
8	87%*	66%

*($p<0.001$ versus ranitidine)

ACIPHEX 20 mg once daily was significantly more effective than ranitidine 150 mg QID in the percentage of patients with complete resolution of heartburn at Weeks 4 and 8 ($p<0.001$). ACIPHEX 20 mg once daily was also more effective in complete resolution of daytime heartburn ($p\leq0.025$), and night time heartburn ($p\leq0.012$) at both Weeks 4 and 8, with significant differences by the end of the first week of the study.

14.2 Long-term Maintenance of Healing of Erosive or Ulcerative GERD

The long-term maintenance of healing in patients with erosive or ulcerative GERD previously healed with gastric anti-secretory therapy was assessed in two U.S., multicenter, randomized, double-blind, placebo-controlled studies of identical design of 52 weeks duration. The two studies randomized 209 and 285 patients, respectively, to receive either 10 mg or 20 mg of ACIPHEX QD or placebo. As demonstrated in the tables below, ACIPHEX was significantly superior to placebo in both studies with respect to the maintenance of healing of GERD and the proportions of patients remaining free of heartburn symptoms at 52 weeks:

TABLE 10 PERCENT OF PATIENTS IN ENDOSCOPIC REMISSION

	ACIPHEX 10 mg	ACIPHEX 20 mg	Placebo
Study 1	N=66	N=67	N=70
Week 4	83%*	96%*	44%
Week 13	79%*	93%*	39%
Week 26	77%*	93%*	31%
Week 39	76%*	91%*	30%

Week 52	73%*	90%*	29%
Study 2	N=93	N=93	N=99
Week 4	89%*	94%*	40%
Week 13	86%*	91%*	33%
Week 26	85%*	89%*	30%
Week 39	84%*	88%*	29%
Week 52	77%*	86%*	29%
Combined Studies	N=159	N=160	N=169
Week 4	87%*	94%*	42%
Week 13	83%*	92%*	36%
Week 26	82%*	91%*	31%
Week 39	81%*	89%*	30%
Week 52	75%*	87%*	29%

*($p<0.001$ versus placebo)

TABLE 11 PERCENT OF PATIENTS WITHOUT RELAPSE IN HEARTBURN FREQUENCY AND DAYTIME AND NIGHTTIME HEARTBURN SEVERITY AT WEEK 52

	ACIPHEX 10 mg	**ACIPHEX 20 mg**	**Placebo**
Heartburn Frequency			
Study 1	46/55 (84%)*	48/52 (92%)*	17/45 (38%)
Study 2	50/72 (69%)*	57/72 (79%)*	22/79 (28%)
Daytime Heartburn Severity			
Study 1	61/64 (95%)*	60/62 (97%)*	42/61 (69%)
Study 2	73/84 (87%)$^{+}$	82/87 (94%)*	67/90 (74%)
Nighttime Heartburn Severity			
Study 1	57/61 (93%)*	60/61 (98%)*	37/56 (66%)
Study 2	67/80 (84%)	79/87 (91%)$^{+}$	64/87 (74%)

* $p\leq0.001$ versus placebo

$^{+}$ $0.001<p<0.05$ versus placebo

14.3 Treatment of Symptomatic GERD

Two U.S., multicenter, double-blind, placebo controlled studies were conducted in 316 patients with daytime and nighttime heartburn. Patients reported 5 or more periods of moderate to very severe heartburn during the placebo treatment phase the week prior to randomization. Patients were confirmed by endoscopy to have no esophageal erosions.

The percentage of heartburn free daytime and/or nighttime periods was greater with ACIPHEX 20 mg compared to placebo over the 4 weeks of study in Study RAB-USA-2 (47% vs. 23%) and Study RAB-USA-3 (52% vs. 28%). The mean decreases from baseline in average daytime and nighttime heartburn scores were significantly greater for ACIPHEX 20 mg as compared to placebo at week 4. Graphical displays depicting the daily mean daytime and nighttime scores are provided in Figures 2 to 5.

FIGURE 2: MEAN DAYTIME HEARTBURN SCORES RAB-USA-2

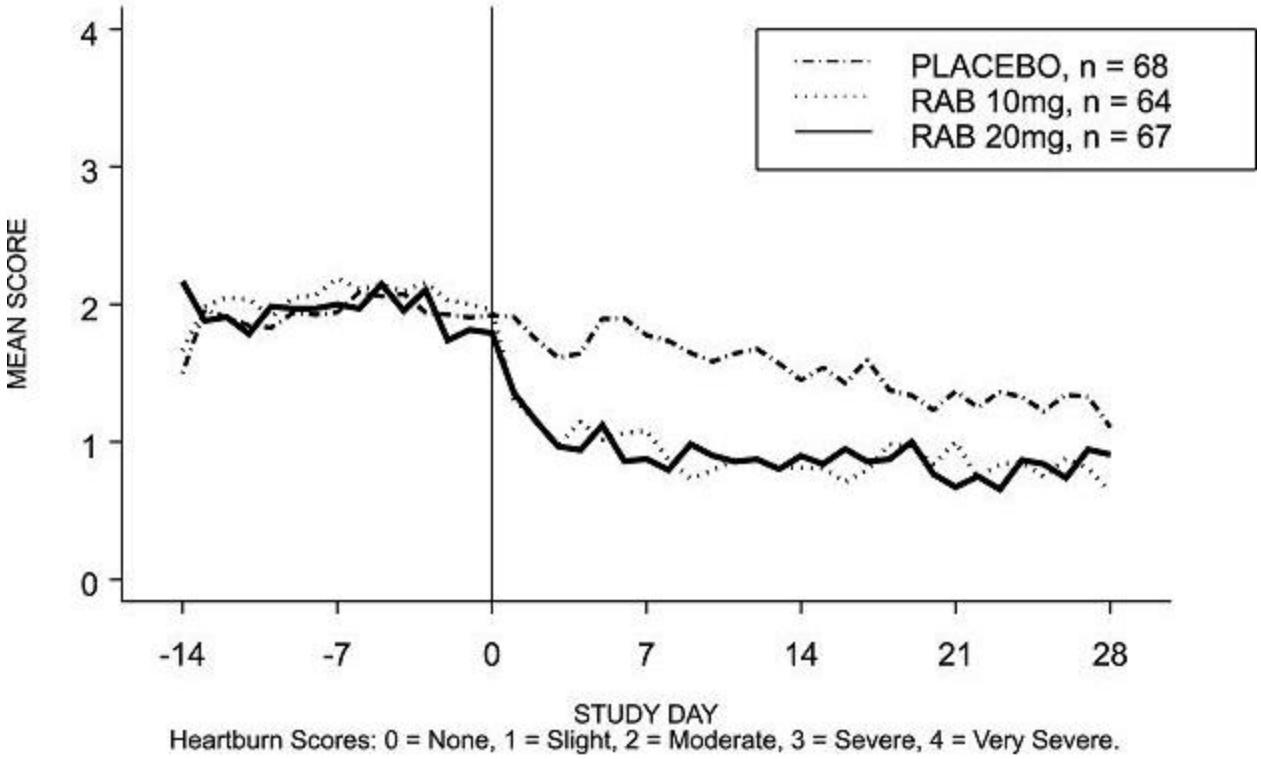


FIGURE 3: MEAN NIGHTTIME HEARTBURN SCORES RAB-USA-2

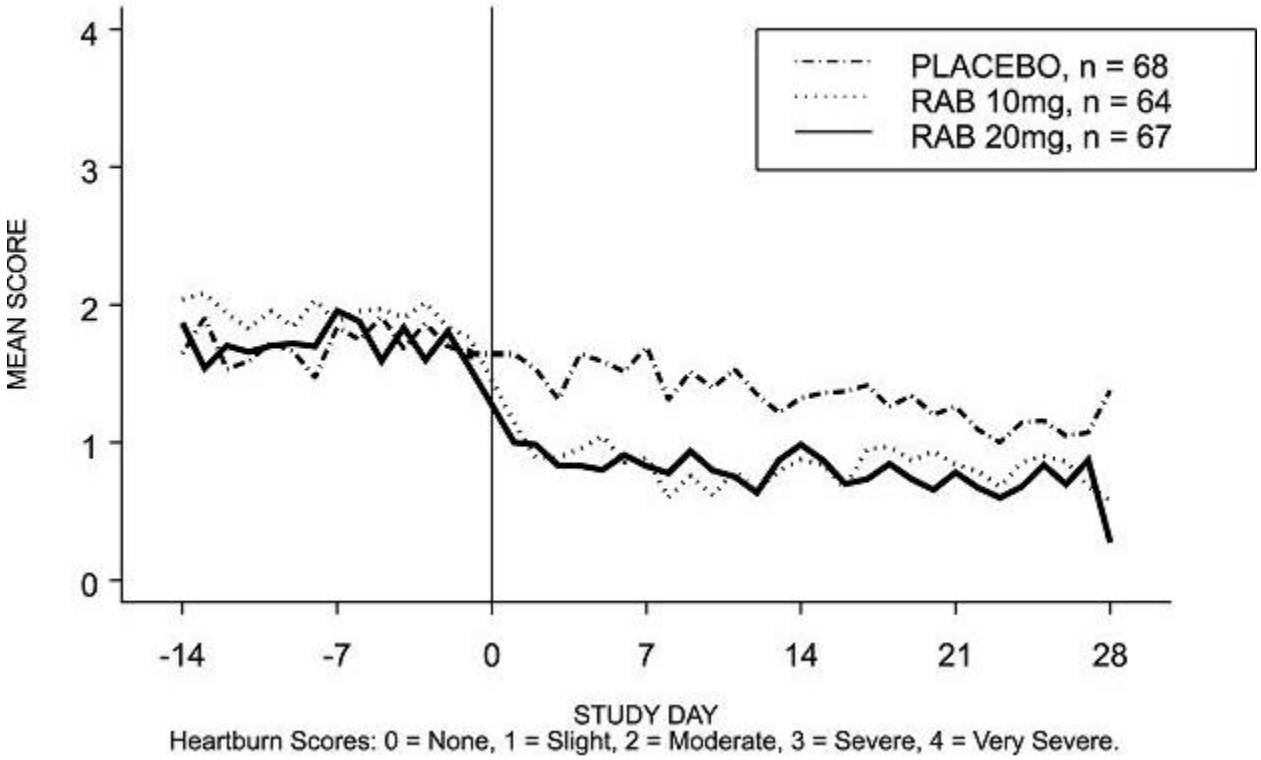


FIGURE 4: MEAN DAYTIME HEARTBURN SCORES RAB-USA-3

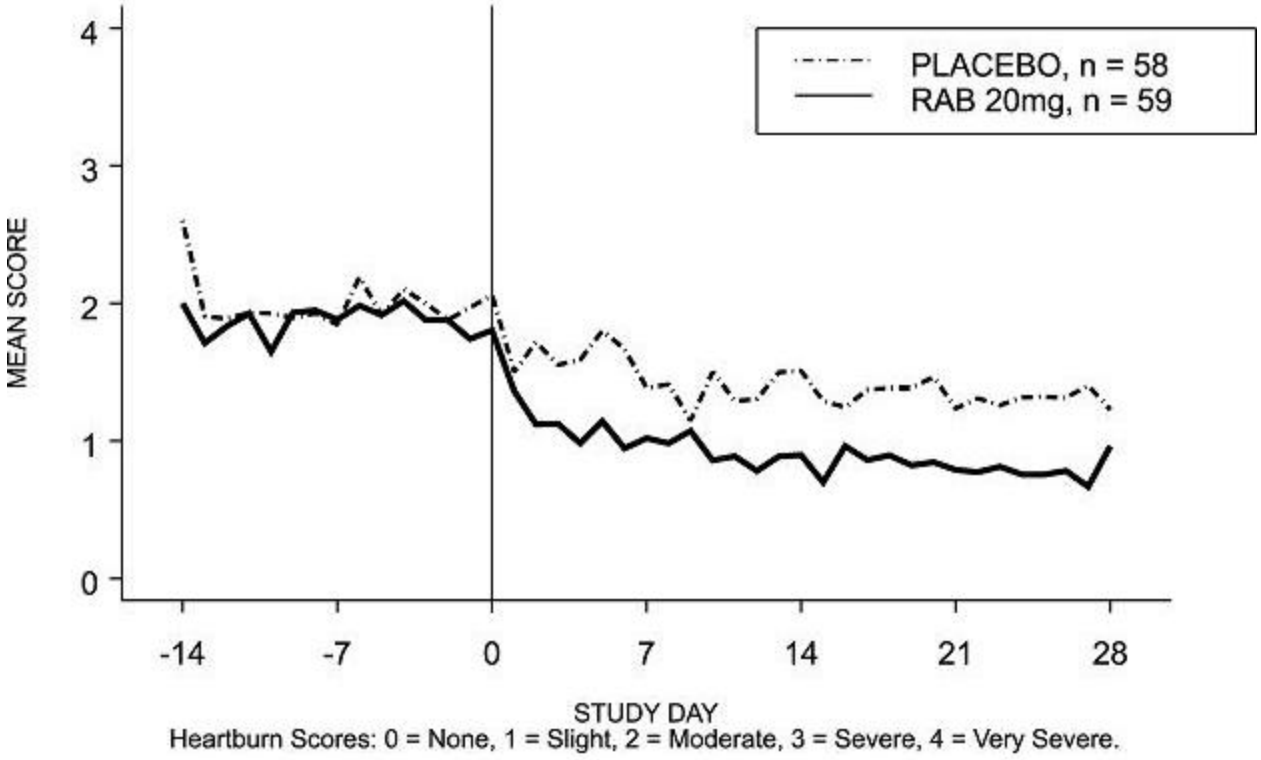
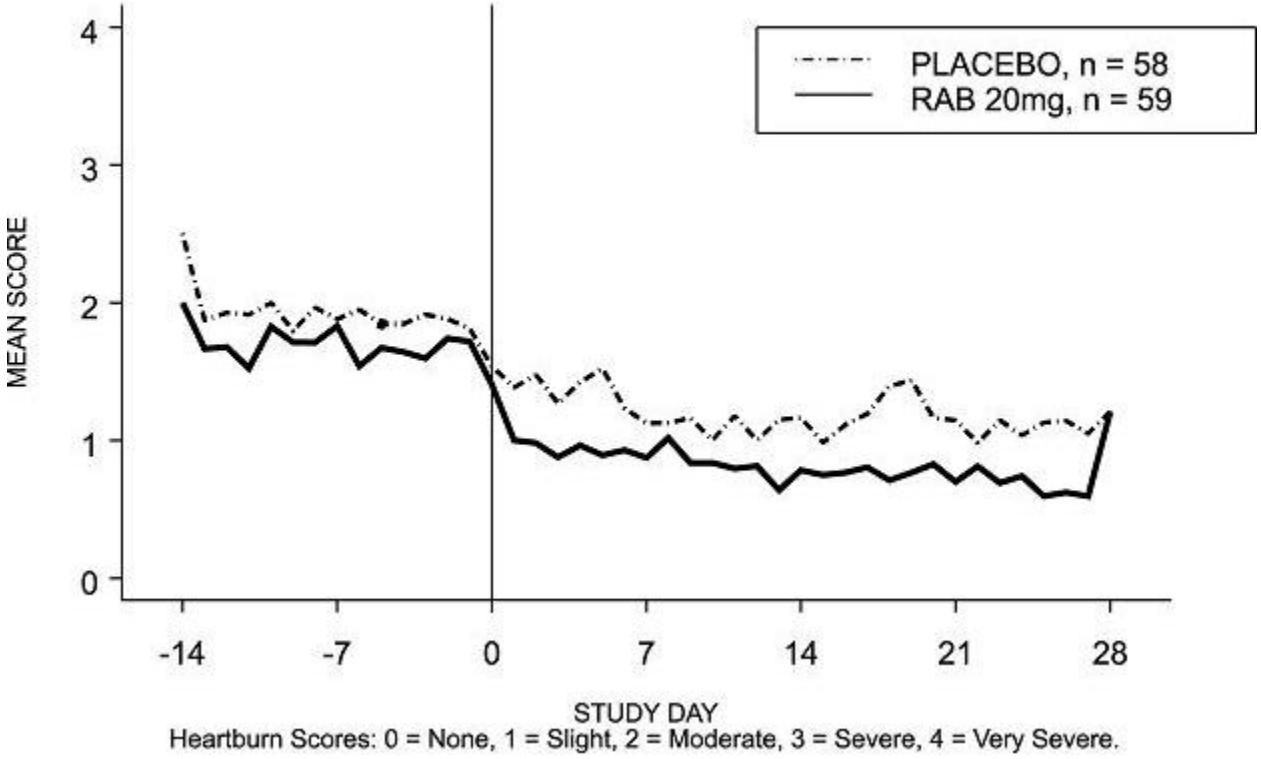


FIGURE 5: MEAN NIGHTTIME HEARTBURN SCORES RAB-USA-3



In addition, the combined analysis of these two studies showed ACIPHEX 20mg significantly improved other GERD-associated symptoms (regurgitation, belching and early satiety) by week 4 compared with placebo (all p values < 0.005).
ACIPHEX 20 mg also significantly reduced daily antacid consumption versus placebo over 4 weeks ($p<0.001$).

14.4 Healing of Duodenal Ulcers

In a U.S., randomized, double-blind, multicenter study assessing the effectiveness of 20 mg and 40 mg of ACIPHEX QD versus placebo for healing endoscopically defined duodenal ulcers, 100 patients were treated for up to four weeks. ACIPHEX was

significantly superior to placebo in producing healing of duodenal ulcers. The percentages of patients with endoscopic healing are presented below:

TABLE 12 HEALING OF DUODENAL ULCERS PERCENTAGE OF PATIENTS HEALED

Week	ACIPHEX 20 mg QD N=34	ACIPHEX 40 mg QD N=33	Placebo N=33
2	44%	42%	21%
4	79%*	91%*	39%

* p≤0.001 versus placebo

At Weeks 2 and 4, significantly more patients in the ACIPHEX 20 and 40 mg groups reported complete resolution of ulcer pain frequency (p≤0.018), daytime pain severity (p≤0.023), and nighttime pain severity (p≤0.035) compared with placebo patients. The only exception was the ACIPHEX 40 mg group versus placebo at Week 2 for duodenal ulcer pain frequency (p=0.094). Significant differences in resolution of daytime and nighttime pain were noted in both ACIPHEX groups relative to placebo by the end of the first week of the study. Significant reductions in daily antacid use were also noted in both ACIPHEX groups compared to placebo at Weeks 2 and 4 (p<0.001).

An international randomized, double-blind, active-controlled trial was conducted in 205 patients comparing 20 mg ACIPHEX QD with 20 mg omeprazole QD. The study was designed to provide at least 80% power to exclude a difference of at least 10% between ACIPHEX and omeprazole, assuming four-week healing response rates of 93% for both groups. In patients with endoscopically defined duodenal ulcers treated for up to four weeks, ACIPHEX was comparable to omeprazole in producing healing of duodenal ulcers. The percentages of patients with endoscopic healing at two and four weeks are presented below:

TABLE 13 HEALING OF DUODENAL ULCERS PERCENTAGE OF PATIENTS HEALED

Week	ACIPHEX 20 mg QD N=102	Omeprazole 20 mg QD N=103	95% Confidence Interval for the Treatment Difference (ACIPHEX - Omeprazole)
2	69%	61%	(-6%, 22%)
4	98%	93%	(-3%, 15%)

ACIPHEX and omeprazole were comparable in providing complete resolution of symptoms.

14.5 *Helicobacter pylori* Eradication in Patients with Peptic Ulcer Disease or Symptomatic Non-Ulcer Disease

The U.S. multicenter study was a double blind, parallel group comparison of rabeprazole, amoxicillin, and clarithromycin for 3, 7, or 10 days vs. omeprazole, amoxicillin and clarithromycin for 10 days. Therapy consisted of rabeprazole 20 mg twice daily, amoxicillin 1000 mg twice daily, and clarithromycin 500 mg twice daily (RAC) or omeprazole 20 mg twice daily, amoxicillin 1000 mg twice daily, and clarithromycin 500 mg twice daily (OAC). Patients with *H. pylori* infection were stratified in a 1:1 ratio for those with peptic ulcer disease (active or a history of ulcer in the past five years) [PUD] and those who were symptomatic but without peptic ulcer disease [NPUD], as determined by upper gastrointestinal endoscopy. The overall *H. pylori* eradication rates, defined as negative ^{13}C-UBT for *H. pylori* ≥ 6 weeks from the end of the treatment are shown in the following table. The eradication rates in the 7-day and 10-day RAC regimens were found to be similar to 10-day OAC regimen using either the Intent-to-Treat (ITT) or Per-Protocol (PP) populations. Eradication rates in the RAC 3-day regimen were inferior to the other regimens.

TABLE 14 HELICOBACTER PYLORI ERADICATION AT ≥ 6 WEEKS AFTER THE END OF TREATMENT

	Treatment Group Percent (%) of Patients Cured (Number of Patients)		Difference (RAC - OAC) [95% Confidence Interval]
	7-day RAC*	**10-day OAC**	
Per Protocol[a]	84.3% (N=166)	81.6% (N=179)	2.8 [- 5.2, 10.7]
Intent-to-Treat[b]	77.3% (N=194)	73.3% (N=206)	4.0 [- 4.4, 12.5]
	10-day RAC*	**10-day OAC**	
Per Protocol[a]	86.0% (N=171)	81.6% (N=179)	4.4 [- 3.3, 12.1]
Intent-to-Treat[b]	78.1% (N=196)	73.3% (N=206)	4.8 [- 3.6, 13.2]
	3-day RAC	**10-day OAC**	
Per Protocol[a]	29.9%	81.6%	-51.6

	(N=167)	(N=179)	[- 60.6, -42.6]
Intent-to-Treat[b]	27.3% (N=187)	73.3% (N=206)	-46.0 [- 54.8, -37.2]

[a] Patients were included in the analysis if they had *H. pylori* infection documented at baseline, defined as a positive ^{13}C-UBT plus rapid urease test or culture and were not protocol violators. Patients who dropped out of the study due to an adverse event related to the study drug were included in the evaluable analysis as failures of therapy.

[b] Patients were included in the analysis if they had documented *H. pylori* infection at baseline as defined above and took at least one dose of study medication. All dropouts were included as failures of therapy.

* The 95% confidence intervals for the difference in eradication rates for 7-day RAC minus 10-day RAC are (-9.3, 6.0) in the PP population and (-9.0, 7.5) in the ITT population.

14.6 Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome

Twelve patients with idiopathic gastric hypersecretion or Zollinger-Ellison syndrome have been treated successfully with ACIPHEX at doses from 20 to 120 mg for up to 12 months. ACIPHEX produced satisfactory inhibition of gastric acid secretion in all patients and complete resolution of signs and symptoms of acid-peptic disease where present. ACIPHEX also prevented recurrence of gastric hypersecretion and manifestations of acid-peptic disease in all patients. The high doses of ACIPHEX used to treat this small cohort of patients with gastric hypersecretion were well tolerated.

15. REFERENCES

1. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*—Fifth Edition. Approved Standard NCCLS Document M7-A5, Vol. 20, No. 2, NCCLS, Wayne, PA, January 2000.

16. HOW SUPPLIED/STORAGE AND HANDLING

ACIPHEX 20 mg is supplied as delayed-release light yellow enteric-coated tablets. The name and strength, in mg, (ACIPHEX 20) is imprinted on one side.
Bottles of 30 (NDC 62856-243-30)
Bottles of 90 (NDC 62856-243-90)
Unit Dose Blisters Package of 100 (10 x 10) (NDC#62856-243-41)
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). [see USP Controlled Room Temperature] Protect from moisture.

17. PATIENT COUNSELING INFORMATION

17.1 How to Take ACIPHEX

Patients should be cautioned that ACIPHEX delayed-release tablets should be swallowed whole. The tablets should not be chewed, crushed, or split. ACIPHEX can be taken with or without food.

17.2 FDA-approved patient labeling
PATIENT INFORMATION
ACIPHEX (a-se-feks)
(rabeprazole sodium)
Delayed-Release Tablets

Read the Patient Information that comes with ACIPHEX before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is ACIPHEX?

ACIPHEX is a medicine called a proton pump inhibitor or an "acid pump inhibitor". This means it reduces the amount of acid that is made by your stomach. ACIPHEX is used in adults:

- for the short-term (4 to 8 weeks) treatment in the healing and symptom relief of damaging (erosive) Gastroesophageal Reflux Disease (GERD).
- to maintain healing of damage (erosions) and relief of heartburn symptoms with GERD. ACIPHEX has not been studied for treatment lasting longer than 12 months (1 year).
- for the treatment of daytime and nighttime heartburn and other symptoms that happen with GERD.
- for short-term treatment (up to 4 weeks) in the healing and relief of stomach-area (duodenal) ulcers. The duodenal area is the area where food passes when it leaves the stomach. The main symptom of a duodenal ulcer is a steady pain in the stomach area.
- with certain antibiotic medicines for the treatment of an infection caused by bacteria called *H. pylori*. Sometimes *H. pylori* bacteria can cause duodenal ulcers. The infection needs to be treated to prevent the ulcers from coming back.

- for the long-term treatment of conditions where your stomach makes too much acid. This includes a condition called Zollinger-Ellison syndrome.

ACIPHEX is used in adolescents 12 years of age and above:
- For the short-term (up to 8 weeks) treatment of GERD.

- The safety and effectiveness of ACIPHEX has not been established for children under the age of 12.

Who should not take ACIPHEX?
Do not take ACIPHEX if you:
- are allergic to any of the ingredients in ACIPHEX. See the end of this leaflet for a complete list of ingredients in ACIPHEX.

- are allergic to any other Proton Pump Inhibitor (PPI) medicine.

What should I tell my doctor before I take ACIPHEX?
Tell your doctor about all of your medical conditions, including if you:
- have any liver problems

- have any allergies

- are pregnant or planning to become pregnant. It is not known if ACIPHEX can harm your unborn baby.

- are breastfeeding. It is not known if ACIPHEX passes into your breast milk or if it can harm your baby. You should choose to breastfeed or take ACIPHEX, but not both. Talk to your doctor about other ways to feed your baby while taking ACIPHEX.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. ACIPHEX and certain medicines can affect each other. This can cause serious side effects. Know the medicines that you take. Keep a list of them with you and show it to your doctor when you get a new medicine. Be sure to tell your doctor if you are taking:
- atazanavir (Reyataz)

- cyclosporine (Sandimmune, Neoral)

- digoxin (Lanoxin)

- ketoconazole (Nizoral)

- warfarin (Coumadin)

- antibiotics

How should I take ACIPHEX?
- Take ACIPHEX exactly as prescribed. Your doctor will prescribe the dose that is right for you and your medical condition. Do not change your dose or stop taking ACIPHEX unless you talk to your doctor. Take ACIPHEX for as long as it is prescribed even if you feel better.

- ACIPHEX is usually taken once a day. Your doctor will tell you the time of day to take ACIPHEX, based on your medical condition.

- ACIPHEX can be taken with or without food. Your healthcare provider will tell you whether to take this medicine with or without food based on your medical condition.

- Swallow each ACIPHEX tablet whole with water. **Do not chew, crush, or split ACIPHEX tablets** because this will damage the tablet and the medicine will not work. Tell your doctor if you cannot swallow tablets whole. You may need a different medicine.

- **If you miss a dose of ACIPHEX, take it as soon as possible. If it is almost time for your next dose, skip the missed dose and go back to your normal schedule. Do not take 2 doses at the same time.**

- If you take too much ACIPHEX, call your doctor or Poison Control Center right away, or go to the emergency room.

- Your doctor may prescribe antibiotic medicines with ACIPHEX to help treat a stomach infection and heal stomach-area (duodenal) ulcers that are caused by bacteria called *H. pylori*. Make sure you read the patient information that comes with an antibiotic before you start taking it.

What are the possible side effects of ACIPHEX?
ACIPHEX, like other proton pump inhibitors, may cause serious allergic reactions. See the end of this leaflet for a complete list of ingredient in ACIPHEX.
The most common side effects with ACIPHEX may include:
- headache
- pain
- pharyngitis
- flatulence
- infection
- constipation

These are not all the side effects of ACIPHEX. For more information, ask your doctor or pharmacist.
Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
How should I store ACIPHEX?
- Store ACIPHEX in a dry place at room temperature, 59°F to 86°F (15°C to 30°C).
- **Keep ACIPHEX and all medicines out of the reach of children.**

General Information about ACIPHEX
Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not use ACIPHEX for any condition for which it was not prescribed by your doctor. Do not give ACIPHEX to other people, even if they have the same symptoms as you. It may harm them.
This leaflet summarizes the most important information about ACIPHEX. If you would like more information, talk to your doctor. You can also ask your doctor or pharmacist for information about ACIPHEX that is written for healthcare professionals. For full product information, visit the website at http://www.aciphex.com/ or call the toll free number 1-888-4-ACIPHEX or 1-800 JANSSEN.
What are the ingredients in ACIPHEX?
Active Ingredient: rabeprazole sodium
Inactive ingredients of the 20 mg tablet are carnauba wax, crospovidone, diacetylated monoglycerides, ethylcellulose, hydroxypropyl cellulose, hypromellose phthalate, magnesium stearate, mannitol, propylene glycol, sodium hydroxide, sodium stearyl fumarate, talc, and titanium dioxide. Iron oxide yellow is the coloring agent for the tablet coating. Iron oxide red is the ink pigment.
The following are registered trademarks of their respective manufacturers:
Reyataz (Bristol-Myers Squibb Company), Sandimmune and Neoral (Novartis Pharmaceuticals Corporation), Lanoxin (GlaxoSmithKline), Nizoral (Janssen Pharmaceutica Products, LP), and Coumadin (Bristol-Myers Squibb Company).
What is GERD?
Your stomach needs acid to help your body digest food. Stomach acid is made by tiny acid pumps in the cells that line your stomach. If your body makes too much acid or cannot protect itself against a normal amount of acid, medical problems such as GERD can happen.
GERD happens when acid in your stomach backs up into the tube (esophagus) that connects your mouth to your stomach. Stomach acid can damage (erode) the lining of your esophagus. Some symptoms of GERD are heartburn, sour taste in the back of your throat and burping.
For prescription only
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ACIPHEX is a registered trademark of Eisai Co., Ltd., Tokyo, Japan.
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